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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/758,962	01/09/2001	Simon Santa-Cruz	00801.0192.NPUS00	9671

22798 7590 11/30/2004

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/758,962	SANTA-CRUZ ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-30,38 and 53-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *38* is/are allowed.

6)☒ Claim(s) *1-5,7-30 and 53-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5, 7-30, 38, 53-56 are pending in the application.

This Office Action is in response to the Amendment filed on 9/20/04.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/6/04 has been entered.

Response to Amendment

The rejection to claims 3 and 4 under 35 U.S.C. 112 1st paragraph is maintained for reason set forth of the record mailed on 10/6/03 and further discussed below.

The rejection to claims 1-3, 5, 7-8, 12-30 and 53-56 under 35 U.S.C.103 (a) is maintained for reasons set forth of the record mailed on 10/6/03 and further discussed below.

The rejection to claims 9-11 under 35 U.S.C.103(a) has been changed to 102 (b) for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3 and 4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to this rejection, Applicants argue that the specification teaches a wide variety of different structures function as an IRES. Applicants argue that the examiner's requirement for naming a core structure is unreasonable for the claimed function since many structures function in the same manner and the structure lacks a core structure. Applicants further indicate that the specification only discloses the chemical structure of IRES using only the broadest definitions as it is a polynucleotide sequence. Applicants thus conclude the written description requirement is met.

The above argument has been fully considered but deemed unpersuasive. As discussed in the previous office actions, the specification needs to describe a representative of species by their complete structure or other identifying characteristics. Although many IRES were known at the time of filing, each distinct IRES (from different species or variants) has its own unique structure (nucleotide sequence). The specification fails to disclose what is the core structure that is shared by these naturally occurring IRES and fragments for its function. Moreover, the specification fails to disclose any specific fragment(s) of said Tobamovirus IRES that is able to direct translation *in vitro*. It is unclear what is the size and which part of the Tobamovirus IRES (SEQ ID NO:1) sequence is necessary for its function. It appears that Applicants misconstrue the examiner's reasoning for the requirement of core structure. Since the claims recite

fragments of naturally occurring IRES, the specification needs describe a representative number of fragments of such IRES that has IRES function. Otherwise, the specification needs describe a core structure for the claimed IRES and fragments so that one skilled in the art would readily recognize this genus of claimed IRES. Such core structure is not necessarily a specific sequence, but some identifying characteristic that is common to the claimed genus of IRES and fragments for their function. Thus, the structure function relationship of the IRES is missing. The definition of the chemical structure of the claimed IRES or fragments being polynucleotide is not sufficient for written description requirement for the claimed invention because not every polynucleotide is a IRES. Therefore, this rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-8, 12-17, 19-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Santa Cruz et al. (1996, PNAS, Vol 93, pp. 6286-6290), in view of Ivanov et al.

Claims 1-3, 5, 18, 30 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ivanov et al., in view of Santa Cruz et al.

In response to this rejection, Applicants argue that Santa Cruz does not teach expression of two separate protein as the claimed invention, whereas Ivanov does not express a viral vector. Applicants thus conclude that the examiner lacks motivation to

expect expression from these two references. Applicants further argue the amended claims add the limitation of IRES is heterologous from the viral vector and /or protein whose expression is controlled by the IRES, and both reference does not teach this limitation. Further, Applicants argue that the teaching of Ivanov reference (specifically abstract, line 11-13, page 40, 2nd col., lines 2-5 and page 41, 2nd col., lines 4-10), does not suggest, motivate and specifically teaches away from using the IRES in any heterologous viral vector system. Applicants further argue that the difference between IRESes discussed in Ivanov further indicates lack of motivation to us an IRES in a heterologous system. Applicants therefore conclude that the invention is not obvious in view of the cited art.

The above arguments have been fully considered but deemed unpersuasive. Contrary to Applicant's assertion, the combined teaching of Ivanov and Santa Cruz provide sufficient motivation to reach the claimed invention. As discussed previously, the teaching of Ivanov demonstrated that crTMV IRES directs translation of a second protein by internal ribosomal entry mechanism. Santa Cruz et al. teach a potato virus X (PVX) based viral vector comprising a green fluorescent protein (GFP) gene linked to CP of the PVX by FMDV 2A peptide (see page 6287, 2nd col., 3rd paragraph). Santa Cruz et al. teach that the FMDV 2A peptide can direct cleavage of the fusion product which would result a GFP and a CP (see page 6287, 2nd col., 4th paragraph). Santa Cruz et al. further teach that this post translational cleavage of polyprotein can be incomplete resulting accumulation of a GFP-2A-CP fusion protein, a GFP-2A fusion protein and PVX CP lacking the first 3 amino acid (see page 6287, 2nd col., 5th paragraph, last two lines). As such, the ordinary artisan would have been motivated to construct a PVX

based viral vector comprising GFP, IRES and CP gene based on the combination teaching of Santa Cruz and Ivanov, because the IRES would increase the expression of the second protein, CP, thus a better strategy for expressing both free GFP and CP than using FMDV 2A peptide. It is unclear why Applicant's would expect no expression at all for the crTMV IRES to function in a plant viral vector. Applicants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to Applicant's argument that Ivanov always uses an IRES that is homologous to both the vector and viral coat protein, the examiner would like to point out this assertion is not entirely true. Ivanov teaches the use of plasmid vector, which is heterologous to the IRES that is from a crTMV virus. Further, whether the coat protein is homologous to the IRES is not relevant to the motivation to combine the reference because this reference discusses in detail of the mechanism of action of the IRES, in which it functions not only to the homologous coat protein, but also heterologous GUS gene (see page 41, 1st col., 2nd paragraph through 2nd col., 1st paragraph). Applicants are reminded that the teaching of the reference should be viewed in context. The examiner cannot agree with Applicant's conclusion that Ivanov teaches away from using their IRES in heterologous viral vector system based on cited passages. The recitation of "the capacity of crTMV IREScp for mediating internal translation distinguishes this CP tobamovirus from the well known type member of the genus TMV U1" in abstract simply teaches that this IREScp can mediate internal translation while the corresponding region from other tobamovirus cannot. Again, the sentences cited by Applicant on page 40 and

41 further state such difference between TMV U1 and crTMV, whereas the latter direct internal ribosomal entry for translation. Ivanov teaches the difference of mechanism of function of the crTMV IRES and other TMV, such as the corresponding region in TMV U1 (not even mentioned as IRES by Ivanov). Ivanov does not teach that the IRES of TMV is incapable of function is crTMV, and certainly never implies that the IREScp from crTMV cannot function in a heterologous fashion. On the contrary, Ivanov teaches it functions not only to the homologous coat protein, but also heterologous GUS gene (see page 41, 1st col., 2nd paragraph through 2nd col., 1st paragraph).

In response to Applicant's assertion that IRES sequences are very different in different virus species, it appears that Applicants have misconstrue the teaching of Ivanov. Ivanov only teaches that nucleotide sequence 150 nt upstream of different tobamovirus CP is different (see Figure 9 legend). Not all of them are IRES because most of them do not direct translation through internal ribosomal entry. Ivanov in fact stresses the unusualness of the crTMV is that its genome comprises this IRES. In fact, just before Applicant's citation on page 42, Ivanov states that "to our knowledge, this study is the first to describe a tobamovirus genome that contains an internal ribosomal entry site." Applicant's quotation #5 simply indicate that the sequence of this IRES is different from other eukaryotic IRES. By Applicant's own admission, many structure of IRES function in same manner (see page 7, 3rd paragraph of the REMARKS). Therefore, such difference does not prevent the crTMV IRES to function in a heterologous vector system. Applicant's quotation #6 simply indicate the similarity of 150 nt region between crucifer-infecting tobamoviruses and different from other tobamoviruses. Again, such statement does not imply in any fashion that the crTMV IRES would not function in a

heterologous vector. Therefore, in view of the combined teaching of Ivanov and Santa Cruz, one of ordinary skilled in the art would have sufficient motivation and expectation of success to reach the claimed invention. Thus, this rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Ivanov et al. (1997, Virology, Vol 232, 32-43).

Ivanov et al. disclose an IRES isolated from Tobamovirus (crTMV) genome, IREScp (see page 40, 2nd col., 3rd paragraph, lines 1-7, also figure 6). Ivanov et al. also disclose a vector, pHΔβNPTCP, which comprising a T7 promoter, inverted tandem repeat, β-sequence of potato virus X, a nucleic acid encoding neomycin phosphotransferase I gene, the IREScp, and the Coat protein (CP) gene of the crTMV (see page 33, 2nd col., 4th paragraph, lines 3-14, and Figure 4). Ivanov et al. also disclose a vector comprising a stable stem loop structure 5' to the IRES, wherein this structure blocked the expression of CP protein expression (see page 39, 1st col., lines 1-4, and Figure 7 A, B, C). The claims are drawn to an IRES capable of directing the expression of an internal ORF in a heterologous viral vector. The claims are further drawn to the crTMV IREScp. Although the function of the crTMV IRES cp for directing expression in heterologous viral vector is not discussed in the reference, it is the inherent function for

said IRES because it has the same structure as the claimed IRES. Therefore, Ivanov et al. disclose the instantly claimed inventions.

Claim 38 is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.